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The IL-6-174C/G polymorphism analysis in Ukrainian residents as prospects for biomedical and pharmacogenetic uses

It is reliably determined that the presence of the *G* allele in the *174C/G* polymorphic region of the *IL-6* gene promoter and a higher level of *IL-6* are more commonly observed among patients suffering from various metabolic disorders and obesity, malignant tumors, type 2 diabetes, periodontitis, oxidative stress. Over time, muscle damage and inflammation processes develop.

Aim. To study the frequency of the *IL-6-174C/G* single nucleotide polymorphism in the Ukrainian population.

Materials and methods. Buccal swab samples for the DNA analysis were collected from 102 healthy volunteers (48 males, 54 females, Ukrainian residents, predominantly ethnical Ukrainians). Genotyping to determine the *IL-6-174C/G* polymorphism was performed on DNA samples from the buccal epithelium using the polymerase chain reaction followed by RELP. Control of the genotype distribution for compliance with the Hardy–Weinberg equilibrium was performed using the χ^2 criterion.

Results and discussion. The distribution of genotypes of the *IL-6-174C/G* polymorphism in the Ukrainian population samples was as follows: *CC* – 46 %, *CG* – 49 %, and *GG* – 5 % of residents. The frequency of the *IL-6-174C/G* polymorphism allele in the population was p_C – 0.71 and q_G – 0.29. The population structure did not deviate from the Hardy–Weinberg equilibrium since there was no difference between the theoretically expected and actual frequencies of three genotypes.

Conclusion. The data obtained demonstrates the presence of the *IL-6-174C/G* polymorphism in the Ukrainian population.

Key words: *IL-6 gene; IL-6-174C/G; polymorphism; Ukraine; allele frequency; Hardy–Weinberg equilibrium*

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Аналіз поліморфізму IL-6-174C/G у мешканців України як перспектива біомедичних та фармакогенетичних варіантів застосування

Достовірно доведено, що наявність алеля G у поліморфній ділянці *174C/G* промотора гена *IL-6* та більш високий рівень *IL-6* частіше спостерігають у пацієнтів із різними метаболічними розладами та ожирінням, злоякісними пухлинами, цукровим діабетом 2 типу, пародонтитом, окислювальним стресом. Згодом розвиваються ураження м'язів і запальні процеси.

Метою нашого дослідження було вивчити частоту однонуклеотидного поліморфізму *IL-6-174C/G* в українській популяції.

Матеріали та методи. У 102 здорових добровольців (48 чоловіків, 54 жінки, жителі України, переважно етнічні українці) взято букальні мазки для аналізу ДНК. Генотипування для визначення поліморфізму *IL-6-174C/G* проводили на зразках ДНК букального епітелію за допомогою полімеразної ланцюгової реакції з подальшим RELP. Контроль розподілу генотипу на відповідність рівновазі Гарді–Вайнберга здійснювали за критерієм χ^2.

Результати. Розподіл генотипів поліморфізму *IL-6-174C/G* у популяційних вибірках України був такий: *CC* – 46 %, *CG* – 49 %, *GG* – 5 % жителів. Частота алеля поліморфізму *IL-6-174C/G* у популяції становить p_C – 0,71 та q_G – 0,29. Структура популяції не відхилялася від рівноваги Гарді–Вайнберга, бо немає різниці між теоретично очікуваною та фактичною частотами трьох генотипів.

Висновок. Отримані дані свідчать про наявність поліморфізму IL-6-174C/G в українській популяції.

Ключові слова: *ген IL-6; IL-6-174C/G; поліморфізм; Україна; частота алелів; рівновага Гарді–Вайнберга*

Introduction. The *IL-6* gene is presented in 7p21 chromosome and consists of four introns and five exons [1]. As the single nucleotide polymorphism can affect both intron and exon areas of a gene, the structural changes can lead both to a change of gene expression and a change in the IL-6 activity. Replacement of cytosine (C) with guanine (G) in the promoter gene region, namely in the 5' flanking region in position 174 is the well-studied *IL-6* gene polymorphism. In this case, the change of the *IL-6* gene transcriptional activity in response to some regulatory factors was described. It is known that people with the *G* allele have higher IL-6 concentrations in the blood compared to people with the *C* allele, which is an alternative for this position [2]. The relationship between the *IL-6* gene polymorphism, the level of the corresponding pro-inflammatory cytokine and clinically significant human traits is still not clear. This may be connected with the fact that IL-6 has both pro-inflammatory and anti-inflammatory features.

It is shown that polymorphism in the *IL-6-174C/G* promoter is associated with metabolic disorders and obesity [3], malignant tumors [4-6], type 2 diabetes [7], hearing loss [8], oxidative stress with subsequent muscle injuries and inflammation processes [9], etc. In particular, some authors discovered relations between *C* allele findings and certain diseases: an active form of toxoplasmosis

with progressive toxoplasmic retinochoroiditis [10], type 2 diabetes [11], sepsis [12]; diseases having a low survival rate: neuroblastoma [6], endometrium adenocarcinoma [13], squamous cell carcinoma of the oral cavity [14], complicated breast cancer [5]. An increased frequency of paranoic schizophrenia, in which a failure of the immune system is observed [15]. On the other hand, the *G* allele is associated with coronary artery disease and hypertensive heart disease [16].

At the same time, there was either no information about associations of the *IL-6-174C/G* polymorphism or that information was contradictory. In particular, during experimentally induced human endotoxemia caused by intravenous administration of lipopolysaccharide, the genotype of the participants did not depend on changes in the level of IL-6 in plasma [17]. There was also no dependence between the *IL-6* gene polymorphism and the risk of multiple myeloma [18], late Alzheimer's disease [19], type 2 diabetes [20], head and neck cancer [4]. Some contradictory information concerning the protective *CC* genotype is present: among Greeks suffering from type 2 diabetes [21].

Materials and methods. In order to study the population distribution of the *IL-6-174C/G* polymorphism, the sample consisted of Ukrainian residents, predominantly ethnical Ukrainians, was selected. Buccal swab samples for the DNA analysis were collected from 102 healthy volunteers (48 males, 54 females) who were not relatives. The material was collected in accordance with ethical standards of work under the Helsinki Declaration (World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects). Genotyping to determine the *IL-6-174C/G* polymorphism was performed on DNA samples from the buccal epithelium using the polymerase chain reaction followed by RELP [22]. DNA was isolated from buccal epithelium samples of the subjects using a Chelex-100 ion-exchange resin [23]. The allelic state of the IL-6 gene was determined by a 174C/G single nucleotide replacement (rs2069840) according to the method [24]. Amplification was performed using a "Tercyc" DNA amplifier (DNA-Technology). To amplify a fragment of the *IL-6* gene containing a polymorphic site (*174C/G*), the forward primer TGACTTCAGCTTTACTCTTTGT and reverse primer AATAGGTTTTGAGGGCCATG were used [25]. Restriction of amplification products was performed using Hin1II endonuclease (NlaIII) (MBI Fermentas, Lithuania). The restriction products were analyzed using electrophoresis in 2 % agarose gel. 1×TBE was used as an electrophoretic buffer. DNA pUC19 hydrolyzed by MspI endonuclease (MBI Fermentas, Lithuania) was used as a molecular weight marker. The visualization of amplification and restriction products was performed by staining a gel with ethidium bromide and photographing on a transilluminator in ultraviolet light. The restriction fragment sizing 164 bps corresponded to the *C* allele of the *174C/G* variant of the *IL-6* gene, while two restriction fragments sizing 112 and 52 bps, respectively, corresponded to the *G* allele.

The frequencies of alleles (*p* and *q*) were calculated according to the results of genotyping:

$$p_C = \frac{2CC + CG}{2N} \text{ and } q_G = \frac{2GG + CG}{2N}$$

where *N* is the number of the study participants.

Control of the genotype distribution for compliance with the Hardy–Weinberg equilibrium was performed using the χ^2 criterion. The statistical hypotheses were verified at a significance level of $p \leq 0.05$.

Results and discussion. Genotyping of subjects for *IL-6-174C/G* polymorphism showed that the study sample had the smallest number of *GG* homozygotes (5 of 102). There was approximately equal amount of *CC* homozygotes and *CG* heterozygotes (*CC* – 47 of 102, *CG* – 50 of 102). Altogether, the percentage distribution of genotypes in the population sample was as follows: *CC* – 46 %, *CG* – 49 %, and *GG* – 5 % of individuals (Table 1).

The frequencies of *C* and *G* alleles were calculated separately for males and females. The average weighted frequencies for the corresponding alleles were also calculated; they were p_C – 0.71 and q_G – 0.29, respectively (Table 2).

According to the frequencies of actual alleles, the frequencies of the corresponding genotypes were calculated based on the Hardy–Weinberg proportion (Table 3).

The theoretically expected frequencies of genotypes calculated using Hardy–Weinberg equations were not statistically significantly different from the observed ones (Table 4). That allows us to conclude that there is an equilibrium in the *IL-6-174C/G* polymorphism in the sample of the Ukrainian population.

The frequencies of indicated alleles were studied in a number of populations. Studies have shown that world population differs by frequency of these alleles.

Table 1

Distribution of the *IL-6-174C/G* polymorphism genotypes

	Males, N	Females, N	Total, N (%)
CC	19	28	47 (46)
CG	26	24	50 (49)
GG	3	2	5 (5)
Statistics: $\chi^2 = 1.656$, df = 2, $p > 0.05$.			

Note. χ^2 – Pearson criterion, df – degree of freedom, p – level of significance.

Table 2

The frequencies of *C* and *G* alleles of the *IL-6-174C/G* polymorphism

	Alleles	
	C	G
Males	0.67	0.33
Females	0.74	0.26
Total	0.71	0.29

Table 3

Genotypes frequencies in the *IL-6-174C/G* polymorphism

	Genotypes		
	CC	CG	GG
Males	0.45	0.44	0.11
Females	0.55	0.38	0.07
Total	0.50	0.42	0.08

Table 4

The theoretically expected frequencies of the *IL-6-174C/G* polymorphism genotypes in the population

	The theoretically expected frequencies of genotypes	The actual frequencies of genotypes
CC	51	47
CG	43	50
GG	8	5
Statistics: $\chi^2 = 1.382$, df = 2, $p > 0.05$.		

In particular, in Brazil one of the studies showed that the *G* allele was major, meanwhile the *C* allele was minor. As a result, in healthy people $p_G = 0.92$ and $p_C = 0.08$; people with the *CC* genotype – 6 %, *GG* – 89.2 % and *CG* – 4.8 %. In the group of patients with toxoplasmatic retinochoroiditis the corresponding frequencies were different: $p_G = 0.83$ and $p_C = 0.17$, *CC* homozygotes – 6.2 %, *GG* homozygotes – 71.1 % and *CG* heterozygotes – 22.7 % [11]. There are data obtained from the study of Greece residents where a sample of 393 patients with type 2 diabetes was studied: the distribution of genotype was as follows: *GG* – 49.1 %, *GC* – 26.8 % and *CC* – 24.1 % of people; genotype frequencies had no gender differences [21]. In India, the frequencies of *CC* homozygotes, *GG* homozygotes and *CG* heterozygotes among the healthy population were 4.9 %, 69.7 %, and 25.4 %; the frequencies of *C* and *G* alleles – 0.18 and 0.82, respectively. Similar indicators in patients with squamous cell carcinoma of the oral cavity were 7.7 %, 55.2 % and 37.1 %; the frequencies of *C* and *G* alleles – 0.26 and 0.74, respectively [14].

It is obvious that *C* and *G* alleles can significantly vary in different groups of polyethnic populations. For instance, in Malaysia, where three main ethnic groups are Malayan, Chinese and Hindu, the frequency of *G* allele in the general population is 0.91, *C* allele – 0.09. At the same time, in the Malayan group the frequency of *G* allele is 0.04, among Hindu – 0.19. However, this allele was not detected in the Chinese population [25]. Previously, the study of the *IL-6-174C/G* polymorphism, was conducted in Ukraine and included cancer patients and healthy individuals. In that work, in contrast to our current study, the *G* allele was predominant in the control group of healthy individuals [26]. However, this fact may be explained by polyethnicity in Ukraine. Due to this, we can observe the vast variation in the ethnic composition in different parts of country, and therefore, we can suggest the genetic polymorphism effect in different genes, theoretically not excluding the *IL-6* gene. The above-mentioned study, which involved cancer patients and healthy individuals, was conducted in the southern part of Ukraine, while the volunteers of our current study were mainly residents of the eastern part of Ukraine. Moreover, the Slavic population from different, but neighboring countries may be very close in ethnic composition, unlike those located in the same country, but geographically distant from each other. Thus, the general conclusion is that the gene frequencies studied and different frequencies of genotypes indicate the population distinctions in the *IL-6-174C/G* polymorphism.

Conclusions and prospects for further research. Our research has demonstrated that the distribution of genotypes of the *IL-6-174C/G* polymorphism in the Ukrainian population sample is as follows: *CC* –46 %, *CG* – 49 % and *GG* –5 % of residents. The frequency of the *IL-6-174C/G* polymorphism alleles in the population was p_C – 0.71 and q_G – 0.29. The population structure does not deviate from the Hardy–Weinberg equilibrium since there is no difference between the theoretically expected and actual frequencies of three genotypes.

Conflict of interests: the authors declare that they have no conflicts of interest.

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